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# Guidance for Industry

## Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (Chronic) Toxicity Testing VICH GL-37

## DRAFT GUIDANCE

***This guidance document is being distributed for comment purposes only***

The objective of this draft guidance is to establish recommendations for internationally harmonized repeat-dose chronic toxicity testing.

Comments and suggestions regarding the document should be submitted to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. All comments should be identified with the Docket No. 2003D-0466.

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VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

**VICH GL37 (SAFETY: REPEAT-DOSE CHRONIC TOXICITY)**
**May 2003**
**For consultation at Step 4 - Draft 1**

# STUDIES TO EVALUATE THE SAFETY OF RESIDUES OF VETERINARY DRUGS IN HUMAN FOOD: REPEAT-DOSE (CHRONIC) TOXICITY TESTING

Recommended for Consultation
at Step 4 of the VICH Process
on 8 May 2003
by the VICH Steering Committee

THIS GUIDANCE HAS BEEN DEVELOPED BY THE APPROPRIATE VICH EXPERT WORKING GROUP AND IS SUBJECT TO CONSULTATION BY THE PARTIES, IN ACCORDANCE WITH THE VICH PROCESS. AT STEP 7 OF THE PROCESS, THE FINAL DRAFT WILL BE RECOMMENDED FOR ADOPTION TO THE REGULATORY BODIES OF THE EUROPEAN UNION, JAPAN AND USA.

# Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (Chronic) Toxicity Testing

# STUDIES TO EVALUATE THE SAFETY OF RESIDUES OF VETERINARY DRUGS IN HUMAN FOOD: REPEAT-DOSE (CHRONIC) TOXICITY TESTING

**This draft guidance, when finalized, will represent the agency's current thinking on the safety of residues of veterinary drugs in human food. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statute(s) and/or regulation(s). If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.**

## 1. INTRODUCTION

### 1.1. Objective of the guidance

A variety of toxicological evaluations are performed to establish the safety of veterinary drug residues in human food. The objective of this guidance is to establish recommendations for internationally harmonized repeat-dose chronic toxicity testing.

**FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.**

### 1.2. Background and scope of the guidance

The current guidance is one of a series of guidances developed to facilitate the mutual acceptance of safety data necessary for the determination of acceptable daily intakes (ADIs) for veterinary drug residues in human food. This guidance was developed after consideration of the current practices for evaluating veterinary drug residues in human food in the EU, Japan, USA, Australia, New Zealand, and Canada. It also took account of available data from sub-chronic and chronic toxicity studies.

While this guidance recommends a framework for chronic toxicity testing of veterinary drugs, it is important that the design of the test remains flexible. This guidance does not preclude the possibility of alternative approaches that may offer an equivalent assurance of safety, including scientifically based reasons as to why chronic toxicity testing may not need to be provided. Within the context of this guidance, tests should be tailored to adequately establish the dose-response relationship a no-observed adverse effect level (NOAEL) for toxicity seen following chronic treatment.

### 1.3. General principles

Adequate toxicity testing should include the administration of repeated doses to assess the effects of prolonged exposure to a parent compound and/or metabolites, to define the toxic effects of compounds following chronic exposure, and to ascertain the highest dose that does not produce

toxicity. Available information on the compound should be utilized in designing the chronic toxicity test. The data obtained in this test may be used to establish a NOAEL for a veterinary drug.

## 2. GUIDANCE

### 2.1. Repeat-dose (chronic) toxicity test

#### 2.1.1. Purpose

Chronic toxicity testing is recommended to (1) define toxic effects based on long-term exposures to the compound and/or its metabolites, (2) identify target organs and toxicological endpoints in relation to dose and/or duration of exposure, (3) determine dosages associated with toxic and biological responses, and (4) establish a NOAEL.

#### 2.1.2. Selection of test species

Species selection should take account relevance to human metabolism, pharmacokinetics and pharmacodynamics. The generally accepted default rodent species recommended is the rat, and the default non-rodent species recommended is the dog.

A review of available data on different chemicals was inconclusive with regard to the selection of the number of species needed for chronic toxicity testing. Further analysis of data may clarify this issue. In Japan, chronic studies are required in two species. However, with appropriate scientific justification, chronic toxicity testing may be carried out in only one species. In the EU and the USA, at least one test species should be used. Chronic testing should be performed in the most appropriate species chosen on the basis of all available scientific data, including 90-day studies. The default species recommended is the rat.

#### 2.1.3. Experimental design

Chronic toxicity tests should be conducted in accordance with Organization for Economic Cooperation & Development (OECD) Test Guideline 452 "Chronic Toxicity Studies."[1]

#### 2.1.4. Pathological examination

Gross necropsy and histopathological examination should be performed in accordance with OECD Test Guidelines 408 ("Repeated Dose 90-day Oral Toxicity Study in Rodents"[2]) and 409 ("Repeated Dose 90-day Oral Toxicity Study in Non-rodents"[3]) with the following amendments:

- the following tissues also should be examined: bone (sternum, femur and joint), clitoral or preputial gland (rodents only), Harderian gland, lachrymal gland, larynx, nasal cavity, optic nerves, pharynx, and Zymbal gland (rodents only).
- for non-rodents, histopathological evaluations should be made on all prescribed tissues plus gross lesions from all animals.

## 3. REFERENCES

1. OECD. 1981. Test Guideline 452. Chronic Toxicity Studies. In: OECD Guidelines for the testing of chemicals. Organization for Economic Cooperation & Development, Paris.

2. OECD. 1998. Test Guideline 408. Repeated Dose 90-day Oral Toxicity Study in Rodents. In: OECD Guidelines for the testing of chemicals. Organization for Economic Cooperation & Development, Paris.

3. OECD. 1998. Test Guideline 409. Repeated Dose 90-day Oral Toxicity Study in Non-rodents. In: OECD Guidelines for the testing of chemicals. Organization for Economic Cooperation & Development, Paris.